

specification, as described below. After a final rejection, amendments may be submitted as a matter of right which comply with requirements as to form or adopt suggestions of the Examiner. MPEP 714.12. This amendment after final rejection is submitted to comply with requirements as to form or adopt suggestions of the Examiner. Reexamination and reconsideration of the application, as amended, are respectfully requested.

2. Formal Matters related to Figures

The Patent Office requested Applicants to confirm that Figure 2H is as intended. Figure 2H (like Figures 2C and 2D) is acknowledged by the Patent Office to show the results of receptor binding assays. Per patent specification at page 40, the receptor binding activities of hTSH analogs were assayed by their ability to *displace* <sup>125</sup>I-bTSH from porcine thyroid membranes (2C) and CHO-JP09 cells (2D, 2H). Since the receptor binding activities of hTSH analogs were assayed by their ability to displace labeled bTSH, Figure 2H conforms to the text of the specification. Thus, Applicants confirm that Figure 2H is as intended.

3. "Modified Wild-type"

There is no dispute that the rejections of the claims under 35 USC 102 and 103 over Campbell et al. are withdrawn, where the invention is related to engineered human TSH superanalogues, as opposed to LH, FSH, and hCG, in response to an election of species requirement. The sole issue remaining in this case is the definiteness of the claims language. The Patent Office rejected the claims under 35 USC 112, 2<sup>nd</sup> paragraph, as being indefinite based on the recitation of "modified wild-type," which the Patent Office found repugnant to the art, and under 35 USC 112, 1<sup>st</sup> paragraph, as having no basis in the specification as originally filed for the term; the Patent Office pointed out that the interview did *not* suggest this term and that the term seems to be self-contradictory. Additionally, the Patent Office rejected the claims under 35 USC 112, 2<sup>nd</sup> paragraph, as being indefinite based on the lack of antecedent basis for "comprising" and suggested that "compared to wild-type human TSH, said modified TSH comprising ..." would be remedial of this point. Also, the Patent Office rejected the claims under 35 USC 112, 2<sup>nd</sup> paragraph, as being indefinite based on the implication in

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"the basic amino acid residues" that the recited residues are the only basic residues in the protein and suggested "said basic amino acid residues." Furthermore, the Patent Office rejected Claims 101-105 and 127-131 under 35 USC 112, 2<sup>nd</sup> paragraph, as being indefinite based on purported lack of clarity regarding how a protein can be "further modified" to have *fewer* than a certain number of amino acid substitutions, and suggested that changing "homology" to "identity" would be partially remedial of this point. Finally, the Patent Office rejected the claims under 35 USC 112, 2<sup>nd</sup> paragraph, as being indefinite based on the recitation of "human," and suggested that "A human thyroid stimulating hormone which differs from the wild-type TSH ..." and then stating what differences are allowed relative to wild-type would be remedial of this point.

35 USC 112, 2<sup>nd</sup> paragraph, says that the claims must be definite. By this amendment, neither narrowing nor broadening, no term is repugnant to the art, any lack of antecedent basis is resolved, any wrongful implication is righted, any lack of clarity about the number of amino acid substitutions is remedied, and any question about the meaning of "human" is provided. This amendment is submitted to comply with requirements as to form or adopt Examiner-made suggestions: "A modified human thyroid stimulating hormone (TSH), which differs from the wild-type human TSH, said modified human TSH comprising ... , wherein by human is meant the number of amino acid substitutions in the wild-type sequence does not exceed one-half the number of amino acid differences at corresponding positions in the TSH subunits between human and a non-human species," to name one claim. Support for the amendment is found throughout the patent specification, for example, at 7, lines 8-24:

By "human" glycoprotein hormone is meant that the number of amino acid substitutions made in the wild-type sequence does not exceed one-half the number of amino acid differences at corresponding positions in the corresponding polypeptide hormones between human and another species. Thus, the modified polypeptide hormone would be considered more like the wild-type polypeptide hormone of the human than the corresponding polypeptide hormone from the non-human species from which the amino acid substitutions are derived, based on the amino acid coding sequence. For example, if there were a total of 20 amino acid differences at corresponding positions in corresponding glycoprotein

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hormones between a human glycoprotein and a bovine glycoprotein hormone, a "human" glycoprotein hormone would be a modified wild-type human hormone which contains 10 or fewer amino acid substitutions within its amino acid sequence which are homologous to the corresponding amino acids in the bovine amino acid sequence. More specifically, the thyroid stimulating hormone, as set forth in the Examples contained herein, would be considered "human" if 20 or more of the 40 total amino acid differences between the  $\alpha$ - and  $\beta$ - subunits of the human and bovine homologs are homologous to the amino acid at the corresponding position in the human thyroid stimulating hormone.

Because the amendment is submitted to comply with requirements as to form or adopt suggestions of the Examiner, entry is respectfully requested. The claims are definite sufficient to make clear the metes and bounds of protection. Accordingly, the definiteness requirements of the Patent Statute are satisfied.

#### CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

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Dated: 8/20/01

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

On this set of pages, the insertions are double underlined while the ~~deletions are struck through~~.

81. (AMENDED) A modified ~~wild-type~~ human thyroid stimulating hormone (TSH), which differs from the having increased TSH activity compared to wild-type human TSH, said modified human TSH comprising an  $\alpha$ -subunit and a  $\beta$ -subunit, said  $\alpha$ -subunit comprising at least three basic amino acids in the  $\alpha$ -subunit at positions selected from the group consisting of positions 11, 13, 14, 16, 17, and 20, wherein by human is meant the number of amino acid substitutions in the wild-type sequence does not exceed one-half the number of amino acid differences at corresponding positions in the TSH subunits between human and a non-human species.

82. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, said  $\alpha$ -subunit further comprising a fourth basic amino acid at a position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

83. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 82, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 11, 13, 16, and 20.

84. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 82, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 11, 13, 17, and 20.

85. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 82, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 13, 14, 16, and 20.

86. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 82, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 13, 14, 17, and 20.

87. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 82, said  $\alpha$ -subunit further comprising a fifth basic amino acid at a position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

88. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 87, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 13, 14, 16, 17, and 20.

89. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 87, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 11, 13, 14, 16, and 20.

90. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 11, 13, 14, 16, 17, and 20.

91. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 13, 16, and 20.

92. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, further modified so that said  $\beta$ -subunit comprises a basic amino acid in the  $\beta$ -subunit in at least one position selected from the group consisting of positions 58, 63, and 69.

93. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 92, wherein said ~~the~~ basic amino acids of the  $\beta$ -subunit are at positions 58, 63, and 69.

94. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 92, wherein a basic amino acid of the  $\beta$ -subunit is at position 58.

95. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 92, wherein a basic amino acid of the  $\beta$ -subunit is at position 63.

96. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 92, wherein a basic amino acid of the  $\beta$ -subunit is at position 69.

97. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, wherein said ~~the~~ basic amino acids are selected from the group consisting of lysine and arginine.

98. (AMENDED) A nucleic acid encoding the modified ~~wild-type~~ human TSH  $\alpha$ -subunit of Claim 81.

99. (PENDING) A vector comprising the nucleic acid of Claim 98, wherein the vector is suitable for expressing the nucleic acid.

100. (PENDING) A host cell comprising the vector of Claim 99, wherein the host cell is suitable for expressing the nucleic acid.

101. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, further modified so that said modified ~~wild-type~~ human TSH has less than five amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

102. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, further modified so that said modified ~~wild-type~~ human TSH has less than four amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

103. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, further modified so that said modified ~~wild-type~~ human TSH has less than three amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

104. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, further modified so that said modified ~~wild-type~~ human TSH has less than two amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

105. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 81, further modified so that said modified ~~wild-type~~ human TSH has complete amino acid sequence identity ~~homology~~ with the corresponding wild-type human TSH in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

106. (AMENDED) A modified ~~wild-type~~ human thyroid stimulating hormone (TSH), which differs from the having increased TSH activity compared to wild-type human TSH, said modified human TSH comprising an  $\alpha$ -subunit and a  $\beta$ -subunit, said  $\alpha$ -subunit comprising a basic amino acid in the  $\alpha$ -subunit in at least one position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20, wherein by human is meant the number of amino acid substitutions in the wild-type sequence does not exceed one-half the number of amino acid differences at corresponding positions in the TSH subunits between human and a non-human species.

107. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, wherein a basic amino acid of the  $\alpha$ -subunit is at position 11.

108. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, wherein a basic amino acid of the  $\alpha$ -subunit is at position 13.

109. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, wherein a basic amino acid of the  $\alpha$ -subunit is at position 14.

110. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, wherein a basic amino acid of the  $\alpha$ -subunit is at position 16.

111. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, wherein a basic amino acid of the  $\alpha$ -subunit is at position 17.

112. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, wherein a basic amino acid of the  $\alpha$ -subunit is at position 20.

113. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, wherein said ~~the~~ basic amino acid is selected from the group consisting of lysine and arginine

114. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, further modified so that said  $\alpha$ -subunit comprises a basic amino acid in at least two positions selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

115. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 114, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 16 and 20.

116. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 114, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 16 and 13.

117. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 114, wherein said ~~the~~ basic amino acids of the  $\alpha$ -subunit are at positions 20 and 13.

118. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 114, wherein said ~~the~~ basic amino acid is selected from the group consisting of lysine and arginine.

119. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, further modified so that said  $\beta$ -subunit further comprises a basic amino acid in the  $\beta$ -subunit in at least one position selected from the group consisting of positions 58, 63, and 69.

120. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 119, wherein said ~~the~~ basic amino acids of the  $\beta$ -subunit are at positions 58, 63, and 69.

121. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 119, wherein a basic amino acid of the  $\beta$ -subunit is at position 58.

122. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 119, wherein a basic amino acid of the  $\beta$ -subunit is at position 63.

123. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 119, wherein a basic amino acid of the  $\beta$ -subunit is at position 69.

124. (AMENDED) A nucleic acid encoding the modified ~~wild-type~~ human TSH  $\alpha$ -subunit of Claim 106.

125. (PENDING) A vector comprising the nucleic acid of Claim 124, wherein the vector is suitable for expressing the nucleic acid.

126. (PENDING) A host cell comprising the vector of Claim 125, wherein the host cell is suitable for expressing the nucleic acid.

127. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, further modified so that said modified ~~wild-type~~ human TSH has less than five amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

128. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, further modified so that said modified ~~wild-type~~ human TSH has less than four amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

129. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, further modified so that said modified ~~wild-type~~ human TSH has less than three amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

130. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, further modified so that said modified ~~wild-type~~ human TSH has less than two amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

131. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 106, further modified so that said modified ~~wild-type~~ human TSH has complete amino acid sequence identity ~~homology~~ with the corresponding wild-type human TSH in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

132. (AMENDED) A modified ~~wild-type~~ human thyroid stimulating hormone (TSH), which differs from the ~~having increased TSH activity compared to~~ wild-type human TSH, said modified human TSH comprising an  $\alpha$ -subunit and a  $\beta$ -subunit, said  $\beta$ -subunit comprising a basic amino acid in the  $\beta$ -subunit in at least one position

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selected from the group consisting of positions 58, 63, and 69, wherein by human is meant the number of amino acid substitutions in the wild-type sequence does not exceed one-half the number of amino acid differences at corresponding positions in the TSH subunits between human and a non-human species.

133. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 132, wherein said ~~the~~ basic amino acids of the  $\beta$ -subunit are at positions 58, 63, and 69.

134. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 132, wherein a basic amino acid of the  $\beta$ -subunit is at position 58.

135. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 132, wherein a basic amino acid of the  $\beta$ -subunit is at position 63.

136. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 132, wherein a basic amino acid of the  $\beta$ -subunit is at position 69.

137. (AMENDED) The modified ~~wild-type~~ human TSH of Claim 132, wherein said ~~the~~ basic amino acids are selected from the group consisting of lysine and arginine.

138. (AMENDED) A nucleic acid encoding the modified ~~wild-type~~ human thyroid stimulating hormone (TSH)  $\beta$ -subunit of Claim 132.

139. (PENDING) A vector comprising the nucleic acid of Claim 138, wherein the vector is suitable for expressing the nucleic acid.

140. (PENDING) A host cell comprising the vector of Claim 139, wherein the host cell is suitable for expressing the nucleic acid.

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CLEAN VERSION OF ENTIRE SET OF PENDING CLAIMS

81. (AMENDED) A modified human thyroid stimulating hormone (TSH), which differs from the wild-type human TSH, said modified human TSH comprising an  $\alpha$ -subunit and a  $\beta$ -subunit, said  $\alpha$ -subunit comprising at least three basic amino acids in the  $\alpha$ -subunit at positions selected from the group consisting of positions 11, 13, 14, 16, 17, and 20, wherein by human is meant the number of amino acid substitutions in the wild-type sequence does not exceed one-half the number of amino acid differences at corresponding positions in the TSH subunits between human and a non-human species.

82. (AMENDED) The modified human TSH of Claim 81, said  $\alpha$ -subunit further comprising a fourth basic amino acid at a position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

83. (AMENDED) The modified human TSH of Claim 82, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 11, 13, 16, and 20.

84. (AMENDED) The modified human TSH of Claim 82, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 11, 13, 17, and 20.

85. (AMENDED) The modified human TSH of Claim 82, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 13, 14, 16, and 20.

86. (AMENDED) The modified human TSH of Claim 82, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 13, 14, 17, and 20.

87. (AMENDED) The modified human TSH of Claim 82, said  $\alpha$ -subunit further comprising a fifth basic amino acid at a position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

88. (AMENDED) The modified human TSH of Claim 87, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 13, 14, 16, 17, and 20.

89. (AMENDED) The modified human TSH of Claim 87, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 11, 13, 14, 16, and 20.

90. (AMENDED) The modified human TSH of Claim 81, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 11, 13, 14, 16, 17, and 20.

11. (AMENDED) The modified human TSH of Claim 81, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 13, 16, and 20.

12. (AMENDED) The modified human TSH of Claim 81, further modified so that said  $\beta$ -subunit comprises a basic amino acid in the  $\beta$ -subunit in at least one position selected from the group consisting of positions 58, 63, and 69.

13. (AMENDED) The modified human TSH of Claim 92, wherein said basic amino acids of the  $\beta$ -subunit are at positions 58, 63, and 69.

14. (AMENDED) The modified human TSH of Claim 92, wherein a basic amino acid of the  $\beta$ -subunit is at position 58.

15. (AMENDED) The modified human TSH of Claim 92, wherein a basic amino acid of the  $\beta$ -subunit is at position 63.

16. (AMENDED) The modified human TSH of Claim 92, wherein a basic amino acid of the  $\beta$ -subunit is at position 69.

17. (AMENDED) The modified human TSH of Claim 81, wherein said basic amino acids are selected from the group consisting of lysine and arginine.

18. (AMENDED) A nucleic acid encoding the modified human TSH  $\alpha$ -subunit of Claim 81.

99. (PENDING) A vector comprising the nucleic acid of Claim 98, wherein the vector is suitable for expressing the nucleic acid.

100. (PENDING) A host cell comprising the vector of Claim 99, wherein the host cell is suitable for expressing the nucleic acid.

21. (AMENDED) The modified human TSH of Claim 81, further modified so that said modified human TSH has less than five amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

22. (AMENDED) The modified human TSH of Claim 81, further modified so that said modified human TSH has less than four amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

23. (AMENDED) The modified human TSH of Claim 81, further modified so that said modified human TSH has less than three amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

DD 104. (AMENDED) The modified human TSH of Claim 81, <sup>wherein</sup> further modified so that said modified human TSH has less than two amino acid substitutions in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

B 105. (AMENDED) The modified human TSH of Claim 81, <sup>wherein</sup> further modified so that said modified human TSH has complete amino acid sequence identity with the corresponding wild-type human TSH in said  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

Sub C2 106. (AMENDED) A modified human thyroid stimulating hormone (TSH), which differs from the wild-type human TSH, said modified human TSH comprising an  $\alpha$ -subunit and a  $\beta$ -subunit, said  $\alpha$ -subunit comprising a basic amino acid in the  $\alpha$ -subunit in at least one position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20, wherein by human is meant the number of amino acid substitutions in the wild-type sequence does not exceed one-half the number of amino acid differences at corresponding positions in the TSH subunits between human and a non-human species.

27 107. (AMENDED) The modified human TSH of Claim 106, <sup>26</sup> wherein a basic amino acid of the  $\alpha$ -subunit is at position 11.

28 108. (AMENDED) The modified human TSH of Claim 106, <sup>26</sup> wherein a basic amino acid of the  $\alpha$ -subunit is at position 13.

B2 29 109. (AMENDED) The modified human TSH of Claim 106, <sup>26</sup> wherein a basic amino acid of the  $\alpha$ -subunit is at position 14.

cont 30 110. (AMENDED) The modified human TSH of Claim 106, <sup>26</sup> wherein a basic amino acid of the  $\alpha$ -subunit is at position 16.

31 111. (AMENDED) The modified human TSH of Claim 106, <sup>26</sup> wherein a basic amino acid of the  $\alpha$ -subunit is at position 17.

32 112. (AMENDED) The modified human TSH of Claim 106, <sup>26</sup> wherein a basic amino acid of the  $\alpha$ -subunit is at position 20.

33 113. (AMENDED) The modified human TSH of Claim 106, <sup>26</sup> wherein said basic amino acid is selected from the group consisting of lysine and arginine.

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114. (AMENDED) The modified human TSH of Claim 106, further modified so that said  $\alpha$ -subunit comprises a basic amino acid in at least two positions selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

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115. (AMENDED) The modified human TSH of Claim 114, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 16 and 20.

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116. (AMENDED) The modified human TSH of Claim 114, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 16 and 13.

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117. (AMENDED) The modified human TSH of Claim 114, wherein said basic amino acids of the  $\alpha$ -subunit are at positions 20 and 13.

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118. (AMENDED) The modified human TSH of Claim 114, wherein said basic amino acid is selected from the group consisting of lysine and arginine.

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119. (AMENDED) The modified human TSH of Claim 106, further modified so that said  $\beta$ -subunit further comprises a basic amino acid in the  $\beta$ -subunit in at least one position selected from the group consisting of positions 58, 63, and 69.

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120. (AMENDED) The modified human TSH of Claim 119, wherein said basic amino acids of the  $\beta$ -subunit are at positions 58, 63, and 69.

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121. (AMENDED) The modified human TSH of Claim 119, wherein a basic amino acid of the  $\beta$ -subunit is at position 58.

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122. (AMENDED) The modified human TSH of Claim 119, wherein a basic amino acid of the  $\beta$ -subunit is at position 63.

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123. (AMENDED) The modified human TSH of Claim 119, wherein a basic amino acid of the  $\beta$ -subunit is at position 69.

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124. (AMENDED) A nucleic acid encoding the modified human TSH  $\alpha$ -subunit of Claim 106.

125. (PENDING) A vector comprising the nucleic acid of Claim 124, wherein the vector is suitable for expressing the nucleic acid.

126. (PENDING) A host cell comprising the vector of Claim 125, wherein the host cell is suitable for expressing the nucleic acid.

D 47<sup>27</sup>. (AMENDED) The modified human TSH of Claim 106, <sup>26 wherein</sup> further modified so  
D that said modified human TSH has less than five amino acid substitutions in said  $\alpha$ -  
subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

D 48<sup>28</sup>. (AMENDED) The modified human TSH of Claim 106, <sup>26 wherein</sup> further modified so  
D that said modified human TSH has less than four amino acid substitutions in said  $\alpha$ -  
subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

D 49<sup>29</sup>. (AMENDED) The modified human TSH of Claim 106, <sup>26 wherein</sup> further modified so  
D that said modified human TSH has less than three amino acid substitutions in said  $\alpha$ -  
subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

D 50<sup>30</sup>. (AMENDED) The modified human TSH of Claim 106, <sup>26 wherein</sup> further modified so  
D that said modified human TSH has less than two amino acid substitutions in said  $\alpha$ -  
subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

D 51<sup>31</sup>. (AMENDED) The modified human TSH of Claim 106, <sup>26 wherein</sup> further modified so  
D that said modified human TSH has complete amino acid sequence identity with the  
corresponding wild-type human TSH in said  $\alpha$ -subunit in positions other than positions  
11, 13, 14, 16, 17, and 20.

B3 Sub c3 132. (AMENDED) A modified human thyroid stimulating hormone (TSH), which  
differs from the wild-type human TSH, said modified human TSH comprising an  $\alpha$ -  
subunit and a  $\beta$ -subunit, said  $\beta$ -subunit comprising a basic amino acid in the  $\beta$ -subunit  
in at least one position selected from the group consisting of positions 58, 63, and 69,  
wherein by human is meant the number of amino acid substitutions in the wild-type  
sequence does not exceed one-half the number of amino acid differences at  
corresponding positions in the TSH subunits between human and a non-human  
species.

53 133. (AMENDED) The modified human TSH of Claim 132, <sup>52</sup> wherein said basic  
amino acids of the  $\beta$ -subunit are at positions 58, 63, and 69.

54 134. (AMENDED) The modified human TSH of Claim 132, <sup>52</sup> wherein a basic  
amino acid of the  $\beta$ -subunit is at position 58.

55 135. (AMENDED) The modified human TSH of Claim 132, <sup>52</sup> wherein a basic  
amino acid of the  $\beta$ -subunit is at position 63.

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136. (AMENDED) The modified human TSH of Claim 132, wherein a basic amino acid of the  $\beta$ -subunit is at position 69.

57  
137. (AMENDED) The modified human TSH of Claim 132, wherein said basic amino acids are selected from the group consisting of lysine and arginine.

58  
138. (AMENDED) A nucleic acid encoding the modified human thyroid stimulating hormone (TSH)  $\beta$ -subunit of Claim 132. 52

139. (PENDING) A vector comprising the nucleic acid of Claim 138, wherein the vector is suitable for expressing the nucleic acid.

140. (PENDING) A host cell comprising the vector of Claim 139, wherein the host cell is suitable for expressing the nucleic acid.

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